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THEDES as a drug product intermediate for improved melt-extrusion processibility of thermally labile active ingredients

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SUMMARY

Hot melt extrusion (HME) is extensively employed in the pharmaceutical industry, but its utilization of heat raises concerns over drugs' thermal stability. Strategies to improve stability and processibility of thermolabile materials via salt formation and co-crystals engineering are found in the literature. In this work, it was attempted to use therapeutic deep eutectic solvents (THEDES) as a mean to achieve improved drug thermal stability through the formation of a charge-assisted strong hydrogen boding network. Thermogravimetric studies on THEDES formed using a thermolabile drug, lidocaine, with different non-steroidal anti-inflammatory agents (NSAIDs) were employed to test this hypothesis. The resulted three THEDESs in this study were all tested to be more thermally stable than the corresponding parent compounds, confirming the stabilizing effect from the THEDES bonding network. This investigation reintroduces THEDES as a drug product intermediate with improved processibility for HME.

Hot melt extrusion (HME) involves pumping a mixture of materials using a set of rotating screws at elevated temperatures then extruding the molten mass through an exit orifice with a controlled geometry. HME is extensively studied to improve drugs' biopharmaceutical behaviours owing to its wide range of drug delivery applications, and scalability. However, the heat employed during HME processing is a major limitation, with regard to ingredient selection, due to possible decomposition of materials at high or, sometimes, even moderate temperatures (Censi et al., 2018). Accordingly, improving thermal stability of drugs can result in expanded candidate pool for HME. Stabilization strategies have been reported in the literature to generally involve formation of a stable hybrid via attachment to a second molecule with superior thermal stability, or through establishment of strong intermolecular bonding network (Yuan et al., 2017), amongst others. Since therapeutic deep eutectic solvents (THEDES) are binary molecular adducts formed through strong hydrogen bonding (HB) intermolecular interactions, this work investigated the potential protective effect of HB network within different Lidocaine (Lido) based THEDES.

MATERIALS AND METHODS

Lido was sourced by TCI chemicals, Japan. Ibu, Flurb and Keto were obtained from Kemprotec Ltd., UK.

THEDES were prepared by heating method. Lido was mixed with either of the selected NSAIDs at 1:1 molar ratio then heated in oil bath at 90 °C for 1 hour. Thermogravimetric analysis (TGA; Q50, TA, UK) was utilized to determine the suitability of preparation conditions (isothermal program, at 90 °C for 1 h.), and

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to test thermal stability of the pure drugs and their THEDES (ramp program, 20 °C/min) form ambient temperature to 300 °C.

One way ANOVA with Tukey's multiple comparison as post hoc was applied for statistical analysis of data using IBM SPSS 20 software.

RESULTS AND DISCUSSION

THEDES formation was successful in all three investigated systems and isothermal TGA results showed negligible weight loss, proving the validity of THEDES preparation method. TGA ramp results provided valuable insights about thermal stability of drugs and the respective THEDES. For comparison purposes, 5% weight loss was marked as the onset of degradation (Abdelquader et al., 2022) and %weight loss at 250 °C was used to calculate the protective effect of THEDES formation, since Lido degraded completely at 250 °C, Fig. 1.

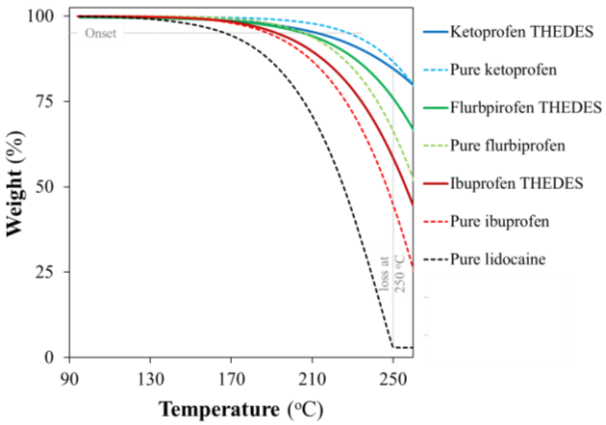

Fig. 1. *TGA profiles of pure drugs and their THEDES.*

$$\Pi_{expected} = (\pi.\gamma)_{Lido} + (\pi.\gamma)_{NSAID} \quad \{Eq.\ 1.\}$$

$$\Omega = ((\Pi_{expected} - \Pi_{actual}) / \Pi_{expected}) \times 100 \quad \{Eq.\ 2.\}$$

THEDES protective effect was calculated according to Eq. 1., 2. where, Π represents total %weight loss at 250 °C, γ is the weight fraction of THEDES component and π is its individual %weight loss at the same temperature, while Ω is the percent weight protected against degradation at 250 °C. Degradation onset of all formed THEDES was significantly (p value < 0.05) higher than Lido or both drugs in case of Ibu THEDES, Fig. 1. and Table 1. In addition, significant (p value < 0.05) protection against degradation at 250 °C (up to 63%) compared to the parent compounds, Table 1. Such results prove the ability of THEDES HB network to extend the processing range of its components without relying on the second molecule stability. Adding this to the versatility of THEDES formers and its plasticization effect can repurpose THEDES as improved candidates for HME (Skowrońska and Wilpiszewska, 2022; Yuan et al., 2017).

Table 1. *Thermal degradation markers of pure drugs and their THEDES.*

Material	Degradation onset (°C)	Ω (%protection at 250 °C)
Pure Lido	170 (3.4)	--
Pure Ibu	186.3 (1.7)	--
Ibu THEDES	199.5 (4.9)	55.4
Pure Flurb	210.5 (6.2)	--
Flurb THEDES	201.7 (12.8)	47.2
Pure Keto	225.4 (2.1)	--
Keto THEDES	207.9 (3.9)	62.7

Values between brackets are standard deviation of three replicates.

CONCLUSIONS

THEDES formation provides an effective protection for drugs against thermal degradation and can extend the thermal processing temperature window.

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